CNT C4

~~29.~~ ~~23.~~ (New) The method of Claim ~~20~~ 26, wherein said antibody to an iron binding protein is an IgG.

REMARKS

Claims 1-10 were at issue. Claims 1-10 were rejected. The Examiner made the following rejections:

(1) The Examiner objects to alleged informalities in the Specification and an alleged lack of descriptiveness in the Title.

(2) Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements / steps.

(3) Claims 1-4, and 7 are rejected under 35 U.S.C. 102(b) as anticipated by U.S. Patent 4,813,399 to Gordon.

(4) Claims 3, 5, and 6[1] are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 4,813,399 to Gordon.

(5) Claims 8-10[2] are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 4,813,399 to Gordon in view of U.S. Patent 4,737,456 to Weng *et al.*

Applicants believe the present amendments and the following remarks traverse the Examiner's rejection of the claims. These remarks are presented in the same order as they appear above.

---

[1] In the Office Action dated 01/17/01, the Examiner appears only to reject Claims 3,5, and 6 under 35 U.S.C. §103 as being unpatentable over Gordon. That is to say the Examiner does not reject the independent "base" claim. Applicants note that it is axiomatic that a dependent claim may not be held obvious if the independent claim from which it depends is **not** obvious.

[2] See, Footnote No. 1.

1. Applicants Are Responsive To The Alleged Informalities Raised By The Examiner

The Applicants have corrected, in the claims, a spelling error and a syntax error identified by the Examiner. In addition, Applicants offer a more descriptive title in view of the Examiner's objections to the title of the application as filed.

2. The Claims Are Definite

The Examiner is reminded that "[c]laims of a patent application *are to be construed in the light of the specification* and the understanding thereof by those skilled in that art to whom they are addressed'." *Application of Salem*, 553 F.2d 676, 683, 193 USPQ 513 (CCPA 1977) (quoting *In re Myers*, 410 F.2d 420, 425 (CCPA 1969) with emphasis added in *Salem*). Furthermore, "[i]f the claims, read in the light of the specifications, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more." *Georgia-Pacific Corp. v. United States Plywood Corp.*, 258 F.2d 124, 136, 118 USPQ 122, 132 (2d Cir.), *cert. denied*, 358 U.S. 884 (1958).

In view of the well established law cited above, Applicants do not agree that, "a detectable marker, which provides for measuring the extent of binding"[3] is an "omitted element"[4] that need be included in the claim. Moreover, Applicants do not agree that independent Claim 1 requires a step, "measuring the extent of binding of iron binding protein to the sample. . .[to indicate]. . .the presence or absence of a demyelinating disease."[5] The specification of the application as filed provides numerous example wherein the Applicants use the binding (or lack thereof) of iron binding proteins to a tissue sample as a means to detect, in a given sample, pathologies consistent with demyelinating diseases.

Indeed, the Applicants use *the lack* of ferritin binding observed in CNS lesions and periplaque margins as a means to detect demyelinating disease. While it is not intended that

---

[3] Office Action mailed 01/17/01, page 3, paragraph 5.

[4] *Id.*

[5] Office Action mailed 01/17/01, page 3, paragraph 6.

the present invention be limited to any one iron binding protein or binding mechanism, in one embodiment the Applicants teach that,

> "ferritin binding is absent within the lesion itself which suggests ferritin is not binding to microglia or astrocytes; the two other types of glial cells found in white matter and which heavily populate the lesion."[6]
>
> * * *
>
> "[t]herefore the present invention contemplates assay systems which are based on the differential binding of ferritin in normal brains and the brains of persons afflicted with MS. In a preferred embodiment, immunocytochemical methods are used identify demyelinated lesions in the brain (consistent with a finding of MS) which substantially fail to bind ferritin."[7]

Conversely, the Applicants use the binding of transferrin in periplaque regions as another means to detect demyelinating disease. Specifically, the Applicants teach that,

> "the normal distributions of transferrin and ferritin binding sites are altered in and around plaques from periventricular white matter isolated from multiple sclerotic (MS) brains. In direct contrast to ferritin binding, transferrin binding in the MS tissue can be seen in white matter periplaque regions and to varying degrees within the lesion itself."[8]

The Applicants, therefore, teach the relative binding of iron binding proteins as an index to differentially detect pathologies consistent with demyelinating disease in a sample from a human suspected of having a demyelinating disease.[9] That is to say, the specification correlates the degree of binding between a human tissue sample and a specific iron binding protein to the detection of a demyelinating disease in a tissue.

---

6 Application as filed, p. 8, ll. 14-16.

7 *Id.* at p. 8, ll. 22-25.

8 *Id* at, p. 8, ll. 6-10.

9 In addition to providing examples of "detectable markers" suited to the methods as claimed. See, for example, application as filed, p. 3, ll. 9-12.

However, in order to advance their business interests and without acquiescing to the Examiner's argument, while expressly reserving the right to prosecute the claims as originally filed (or claims similar thereto), Applicants have amended Claim 1. Specifically, Applicants have linked the method of detection recited in the preamble of these independent claims with an affirmative detection step as set out in section "c)" of the amended claim. In this respect, the claim (read in view of the Specification) particularly points out and distinctly claims the subject matter which the Applicants view as their invention.

Applicants have added "new" Claims 11-23 to the present invention. These new claims recite alternative embodiments of the invention disclosed in the application as filed and, therefore, offer no matter.

3. The Claims Are Not Anticipated

It is well settled law that, under 35 U.S.C. §102, anticipation, "requires that each and every element of the claimed invention be disclosed in the prior art. . . . [i]n addition, the prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public." *Akzo N.V. v. U.S. International Trade Commission*, 1 USPQ 2d 1241, 1245 (Fed. Cir. 1986), *cert. denied*, 482 U.S. 909 (1987). Furthermore, "[t]he Examiner bears the burden of presenting at least a *prima facie* case of anticipation." *In re Sun*, 31 USPQ 2d 1451, 1453. The Applicants submit the Examiner has failed to make a *prima facie* case of anticipation. That is to say, none of the art cited by the Examiner in the instant Action discloses each and every element of the invention as claimed.

A. The Invention as Claimed is Not Anticipated by U.S. Patent 4,813,399 to Gordon.

As a threshold objection, Applicants note that Gordon is ostensibly directed *to therapeutic* methods.

More specifically Gordon teaches a therapeutic regimen wherein,

> "[t]he subject receives an **intravenous injection** or direct injection of a colloidally suspended particle such as iron porphyrin (FeTPPS4) at a dosage of 2-10 mg/kg. After a prescribed period of time which is dependent on the method of introduction of the particles i.e. after 24 hours-14 days after intravenous injection and 20 hours-10 days after direct injection, the subject is exposed to an alternating electromagnetic field at a frequency of 1 Hz to 100 MHz in this case 500 Hz for a period of approximately 10-20 minutes. The alternating electromagnetic field may be applied via a coil arrangement or via capacitor plates or via electrodes in the tissue or any suitable means available in the state of the art, and consistent in application to this present invention. The process may be repeated as is necessary."[10]

The magnetic mapping of iron containing particles, taken up by neuronal cells *in vivo*, may be used as an index to evaluate the physiology of these same cells in real time. More specifically it is the uptake, *in vivo*, of iron containing particles (by neuronal and glial cells) that is taught as a diagnostic method by Gordon. That is to say, the only diagnostic teaching provided by Gordon is expressly limited to this uptake and magnetic mapping facet of Gordon's disclosure.

However, the Examiner states that Gordon teaches "a method for the diagnosis of demyelinating disease using direct contact of a tissue sample with an iron binding protein. . .(see abstract column 9 lines 30-36, claims 1, 46)."[11] Turning to this section of the Gordon patent cited by the Examiner, however, Gordon actually teaches that,

> "[t]hrough the use of magnetic susceptibility measurements. . .the uptake of particles in the neuronal cells and glial cells can be followed as a function of time. *This* may be used diagnostically to evaluate which neurons are affected by the disease process and by analyzing which cells take up the particles. The magnetic characteristics of the particle in the neuronal cell can be used to help diagnose which disease process is present in the neurological tissue. Magnetic mapping techniques can also be used."[12] (emphasis added).

---

[10] U.S. Patent 4,813,399 to Gordon, Column 8, ll. 1-7.

[11] Office Action Mailed January 17, 2001, p. 4, ¶ 8.

[12] U.S. Patent 4,813,399 to Gordon, Column 9, ll. 29-38.

Unlike the present invention, Gordon is silent on a diagnostic method for the detection of demyelinating disease which *measures in vitro the extent of binding* of an iron binding protein to a sample from a human suspected on having a demyelinating disease. As noted above, the diagnostic method suggested by Gordon is limited to use of magnetic susceptibility measurements in connection with the *in vivo* uptake, in neuronal and glial cells, of iron containing particles over time. In this respect the disclosure provided by Gordon fails to teach each and every element of the invention as claim. The Applicants have underscored this deficiency in Gordon, in order to advance their business interests while expressly reserving the right to pursue the claims as filed (or claims similar thereto) in a subsequently filed Continuation application(s), by amending Claim 1 to highlight the reaction of a sample with an iron binding protein *in vitro*.

4. The Claims Are Not Obvious Under 35 U.S.C. § 103(a)

A. The Examiner Fails to Make A *Prima Facie* Case of Obviousness

Claims 1, 3 and 4 - 7 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. patent 4,813,399 to Gordon. Claims 8-10 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. patent 4,813,399 to Gordon and further in view of U.S. patent 4,737,456 to Weng *et al.* The Examiner is reminded that a *prima facie* case of obviousness requires citation to a combination of references which (a) disclose the elements of the claimed invention, (b) suggests or motivates one of skill in the art to combine those elements to yield the claimed combination, and (c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of the these three requirements precludes a finding of a *prima facie* case of obviousness, and, without more, entitle the Applicants to allowance of the claims in issue. *See, e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990).

The Applicants respectfully submit the Examiner has failed to establish any of the three elements of a *prima facie* case of obviousness. In addressing this rejection, Applicants focus on independent Claim 1 since non-obviousness of an independent claim necessarily leads to non-obviousness of claims dependent therefrom. See, MPEP 2143.03.

B. The Cited Art Is Deficient

i. The Examiner Admits That The Cited Art Is Deficient But Has Not Cited To Specific References To Supply The Missing Elements

The Examiner admits that the cited art is deficient. Specifically, in rejecting Claims 1, 3, 5, and 6 the Examiner admits that Gordon "does not indicate the source of ferritin as being native or recombinant"[13] The Examiner does not cite to any additional art to remedy these deficiencies. Rather, the Examiner offers an unsupported conclusion:

> "it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to use native or recombinant or even organically synthesized for that purpose ferritin. . .the skilled artisan would be motivated to use any readily available source of ferritin, which includes recombinant and native forms."

The Applicants respectfully submits that the Examiner's rejection cannot stand without a proper citation to a reference. The Examiner's own bald conclusions cannot serve to create prior art. Indeed, the requirement that the Examiner make a showing of a suggestion, teaching or motivation is "an essential evidentiary component of an obviousness holding." *C.R. Bard, Inc. v. M3 Sys. Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998).

There are three sources for this evidentiary component: the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996). The suggestion most often comes from the teachings of the pertinent references. *In re Rouffet*, 149 F.3d 1350, 1359 (Fed. Cir. 1998). Nonetheless, regardless of the source of the requisite evidence, the Examiner's showing "must be clear and particular, and broad conclusory statements . . . standing alone, are not 'evidence'." *In re Dembiczak*, 175 F.3d 994, 1000 (Fed. Cir. 1999).

It is the Examiner's burden to present "evidence" and this showing must be "clear and particular." Importantly, since an Examiner is NOT one skilled in the art (under the law), the Examiner's opinion on what one skilled in the art might believe does not count. *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993) ("[T]he examiner's assumptions do not constitute the disclosure of the prior art.").

---

[13] Office Action mailed 01/17/01, p. 5, ¶ 9.

Of course, if the Examiner has knowledge of relevant facts which are used to make the rejection, the Examiner is free to used those facts - but only if submitted in the form of an affidavit. *See* 37 CFR 1.107(b). In the present case, the Examiner has submitted no such affidavit.

C. No Motivation to Combine the References

A proper analysis, in view of 35 U.S.C. §103, demands the references cited by the Examiner be considered as whole and must suggest the desirability and, thereby, the obviousness of making the combination. *Hodash v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143, n. 5, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986). Applicant submits that references cannot be considered collectively until the Examiner points to some motivation to combine said references. This analysis prevents the Examiner from using the instant Specification to reconstruct, in hindsight, the invention as claimed. The Federal Circuit, in a recent decision, articulated the policy behind this analysis:

> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

See In re Rouffet et al., 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998).

None of the prior art cited by the Examiner suggests the desirability of making the combination of elements which recapitulates the invention as claimed. In the Office Action mailed on January 17, 2001 the Examiner stated,

> "[i]t would have been prima facie obvious to a person of ordinary skill in the art to modify the iron binding protein of Gordon by labeling it with an autoradiographic or immunofluorescent marker, as shown by Weng et al. in order to attain the well know and widely disclosed advantage of being able to detect the product easily in assays."[14]

---

[14] *Id.* at ¶ 10.

The Applicant respectfully submits the Examiner, once again, presents bald conclusions in place of reasoned motivation, as articulated by the Federal circuit, to combine the cited art.

Weng *et al.* are completely silent the linking (or detection) of an iron containing proteins to any type of detectable marker. Despite this shortcoming, the Examiner suggests that (as set out in the paragraph above) disclosure of a detectable marker incorporated into *any* ligand-receptor binding assay is sufficient to suggest the combination of the cited prior art. The *Rouffet* court, however, admonishes against such an unsupported statement. Indeed, the Federal Circuit stated:

> The Board did not . . . explain what specific understanding or technological principal within the knowledge of one of ordinary skill in the art would have suggested the combination. Instead, the Board merely invoked the high level of skill in the art. If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technological advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness. *Rouffet*, 47 USPQ2d at 1458.

Contrary to the Examiner's opinion, the prior art provides no motivation to combine the references to teach the claimed invention. That is to say, the generic disclosure of radioisotopes and florescent dyes incorporated into ligand-receptor binding assays (e.g. Weng et. al.) *does not* render obvious the specific incorporation of labeled iron containing proteins into the present methods for the detection of demyelinating disease.

D. The Combined References Do Not Teach Each Element of the Claims

Even if the references are improperly combined, the references do not teach each and every element of the invention as claimed. The references cited by the Examiner do not teach a method for the detection of a demyelinating disease comprising: providing: i) a sample from a human suspected of having a demyelinating disease, and ii) iron binding protein; reacting said sample with said iron binding protein *in vitro*; measuring the extent of binding

of said iron binding protein to said sample; under conditions such that a demyelinating disease is detected.

In sum, the Examiner only provides opinion and conclusory statements in support of the pending obviousness rejections. These opinions and conclusions may not be considered "evidence" and, in view of the above-cited case law, and are inadequate to sustain a rejection under 35 U.S.C. § 103. Accordingly, the claims are not obvious and should be passed to allowance.

CONCLUSION

Applicant believes that the arguments set forth above traverse the Examiner's rejections and therefore request that these grounds for rejection be withdrawn for the reasons set forth above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect at 617.252.3353.

Dated: May 17, 2001

Peter G. Carroll
Registration No. 32,837

MEDLEN & CARROLL, LLP
220 Montgomery Street, Suite 2200
San Francisco, California 94104

APPENDIX I
MARKED-UP VERSION OF REWRITTEN, ADDED, AND/OR CANCELLED CLAIMS

The Following is a version of the claims pursuant to 37 C.F.R. § 1.121(c)(1)(ii), please find a set of claims showing all changes made to the pending claim set.

Please amend the following claims:

1. (Amended) A method for the detection of a demyelinating disease comprising:

a) providing: i) a sample from a human suspected of having a demyelinating disease, and ii) iron binding protein;

b) reacting said sample with said iron binding protein <u>in vitro</u>; and

c) measuring the extent of binding of said iron binding protein to said sample, <u>under conditions such that a demyelinating disease is detected.</u>

8. (Amended) The method of Claim 7, wherein said marker is selected from the group consisting of radioisotope and [florescent] <u>fluorescent</u> dye.

10 (Amended) The method of Claim 1, wherein said measuring [if] <u>is</u> performed with a technique selected from the group of autoradiography and immunofluorescence.

Please add the following claims:

11. (New) A method for the detection of a demyelinating disease comprising:

a) providing: i) a sample from a human suspected of having a demyelinating disease, and ii) iron binding protein wherein said iron binding protein is linked to a detectable marker;

b) reacting said sample with said iron binding protein in vitro; and

c) measuring the extent of binding of said iron binding protein to said sample, under conditions such that a demyelinating disease is detected.

12. (New) The method of Claim 11, wherein said sample is brain tissue.

13. (New) The method of Claim 12, wherein said brain tissue is collected *via* surgical biopsy.

14. (New) The method of Claim 11, wherein said iron binding protein is ferritin.

15. (New) The method of Claim 14, wherein said ferritin is native.

16. (New) The method of Claim 14, wherein said ferritin is recombinant.

17. (New) The method of Claim 11, wherein said marker is selected from the group consisting of radioisotope and florescent dye.

18. (New) The method of Claim 17, wherein said radioisotope is ^{125}I.

19. (New) The method of Claim 11, wherein said measuring is performed with a technique selected from the group of autoradiography and immunofluorescence.

20. (New) A method for the detection of a demyelinating disease comprising:

a) providing: i) a sample from a human suspected of having a demyelinating disease, and ii) an antibody reactive with an iron binding protein;

b) reacting said sample with said antibody in vitro; and

c) measuring the extent of binding of said antibody to said sample, under conditions such that a demyelinating disease is detected.

21. (New) The method of Claim 20, wherein said sample is brain tissue.

22. (New) The method of Claim 21, wherein said brain tissue is collected *via* surgical biopsy.

23. (New) The method of Claim 20, wherein said antibody to an iron binding protein is an IgG.

APPENDIX II

CLEAN VERSION OF THE ENTIRE SET OF PENDING CLAIMS AS AMENDED IN THIS COMMUNICATION

1. (Amended) A method for the detection of a demyelinating disease comprising:

a) providing: i) a sample from a human suspected of having a demyelinating disease, and ii) iron binding protein;

b) reacting said sample with said iron binding protein in vitro; and

c) measuring the extent of binding of said iron binding protein to said sample, under conditions such that a demyelinating disease isdetected.

2. The method of Claim 1, wherein said sample is brain tissue.

3. The method of Claim 2, wherein said brain tissue is collected *via* surgical biopsy.

4. The method of Claim 1, wherein said iron binding protein is ferritin.

5. The method of Claim 4, wherein said ferritin is native.

6. The method of Claim 4, wherein said ferritin is recombinant.

7. The method of Claim 4, wherein said ferritin is linked to a detectable marker.

8. (Amended) The method of Claim 7, wherein said marker is selected from the group consisting of radioisotope and fluorescent dye.

9. The method of Claim 8, wherein said radioisotope is ^{125}I.

10. (Amended) The method of Claim 1, wherein said measuring is performed with a technique selected from the group of autoradiography and immunofluorescence.

11. (New) A method for the detection of a demyelinating disease comprising:

a) providing: i) a sample from a human suspected of having a demyelinating disease, and ii) iron binding protein wherein said iron binding protein is linked to a detectable marker;

b) reacting said sample with said iron binding protein in vitro; and

c) measuring the extent of binding of said iron binding protein to said sample, under conditions such that a demyelinating disease is detected.

12. (New) The method of Claim 11, wherein said sample is brain tissue.

13. (New) The method of Claim 12, wherein said brain tissue is collected *via* surgical biopsy.

14. (New) The method of Claim 11, wherein said iron binding protein is ferritin.

15. (New) The method of Claim 14, wherein said ferritin is native.

16. (New) The method of Claim 14, wherein said ferritin is recombinant.

17. (New) The method of Claim 11, wherein said marker is selected from the group consisting of radioisotope and florescent dye.

18. (New) The method of Claim 17, wherein said radioisotope is ^{125}I.

19. (New) The method of Claim 11, wherein said measuring is performed with a technique selected from the group of autoradiography and immunofluorescence.

20. (New) A method for the detection of a demyelinating disease comprising:

a) providing: i) a sample from a human suspected of having a demyelinating disease, and ii) an antibody reactive with an iron binding protein;

b) reacting said sample with said antibody in vitro; and

c) measuring the extent of binding of said antibody to said sample, under conditions such that a demyelinating disease is detected.

21. (New) The method of Claim 20, wherein said sample is brain tissue.

22. (New) The method of Claim 21, wherein said brain tissue is collected *via* surgical biopsy.

23. (New) The method of Claim 20, wherein said antibody to an iron binding protein is an IgG.